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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,751	07/06/2001	Keith D. Allen	R-386	4567

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DELTAGEN, INC.
1003 Hamilton Avenue
Menlo Park, CA 94025

EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 06/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,751	ALLEN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11 October 2001 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-16 are pending examination.

Drawings

In the response, please submit a response to the PTO 498. If the reply to the instant action does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the term "such" on line 5 page 57. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: misspelling of the word "GenBank", page 7, lines 9 and 11 (see http://www.ncbi.nlm.nih.gov/**Genbank**/). These and any other, spelling errors should be corrected in response to this office action. Applicant is encouraged to review the specification for additional spelling errors.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, as best understood, is readable on a genus of a targeting construct comprising: a first polynucleotide sequence homologous to a serine protease and a second polynucleotide sequence homologous to the serine protease, wherein the genus of a targeting construct is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8 and 9, as best understood, is readable on a genus of a non-human transgenic animal comprising a disruption in a serine protease gene, wherein the genus of a non-human transgenic animal is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Furthermore, claim 16, as best understood, is readable on a genus of an agent that modulates the function of a serine protease, wherein the genus of an agent not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at

the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of targeting constructs comprising: a first polynucleotide sequence homologous to a serine protease and a second polynucleotide sequence homologous to the serine protease. The as-filed specification states that, "serine protease gene" refers to a sequence comprising SEQ ID NO: 1 or comprising the sequence encoding the serine protease gene identified in GenBank Accession No. AF042822" (page 7). In addition, the disclosure defines "homologous" as a characteristic of a DNA sequence having at least 70% sequence identity as compared to a reference sequence (page 6). The specification provides sufficient description of sub-species of a targeting vector comprising SEQ ID NO: 3 and 4 (see Figure 2B). However, the as-filed specification does not provide an adequate written description of a representative number of species of targeting constructs comprising a first polynucleotide sequence homologous to a serine protease and a second polynucleotide sequence homologous to the serine protease. It is apparent from the state of the prior art exemplified by Ngo *et al.* (The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, 1994, pp. 491-494) and Chiu *et al.* that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence. This essential element (starting material) that is required for an adequate description of a representative number of species as embraced by the claimed genus of targeting constructs is neither described sufficiently in the specification nor

conventional in the prior art. A mere statement asserting that any polynucleotide sequence homologous to a serine protease and a second polynucleotide sequence homologous to the serine protease without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of targeting constructs as claimed, particularly since the essential element of the coding of a protein or variant thereof other than SEQ ID NOs: 3 and 4, that is yet be discovered is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of (e.g. allelic variants, orthologs, at least 70% homology to a reference sequence, etc.) encoded sequence with homology to a serine protease gene on the basis of the only disclosure of SEQ ID NOs: 3 and 4.

The specification contemplates a genus of transgenic animals comprising a disruption in a serine protease gene. The starting material for making a transgenic animal is a targeting construct described above. The specification provides sufficient description of sub-species of a targeting vector and LacZ expression in a mouse comprising the targeting construct, however, the as-filed specification does not provide sufficient description of any transgenic non-human animal comprising a disruption in a serine protease gene and its corresponding phenotype. Therefore, in view of the lack of sufficient description of the corresponding phenotype, one skilled in the art could not envision the phenotype of any transgenic animal comprising a disruption in a serine protease gene.

In addition, the as-filed specification contemplates that a genus of agents can be identified or developed by using model non-human transgenic animal (page 11). However, it is

apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of an agent as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of agents that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of an agent and/or a non-human transgenic animal and/or a targeting construct. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified agents and/or targeting constructs and/or non-human transgenic animals that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus a targeting construct and/or an agent and/or a non-human transgenic

animal that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of an agent that modulates the function of a serine protease and/or a genus of a non-human transgenic animal comprising a disruption in a serine protease gene and/or a targeting construct comprising a first polynucleotide sequence homologous to a serine protease and a second polynucleotide sequence homologous to the serine protease), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. used for treating a mammal with a disruption in a serine protease gene and/or used for producing a

transgenic animal and/or for use in identifying agents that modulate the function of a serine protease gene, respectively.

The as-filed specification contemplates making and/or using a targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker. The disclosure states that, "the serine proteases are a large family of proteolytic enzymes that include the digestive enzymes, trypsin, and chymotrypsin, components of the complement cascade and of the blood-clotting cascade" (page 1). The as-filed specification defines a serine protease gene as the polynucleotide sequence set forth in SEQ ID NO: 1. The specification states that a mouse gene encoding a new type of membrane bound serine protease (epithin, SEQ ID NO: 1) was isolated and sequenced by Kim et al. (IDS, 1999), see page 2. Kim teaches that, "The sequence was shown to be highly expressed in a thymic epithelial nurse cell line." Kim further teaches that they suspect that epithin will target either an extracellular matrix or another membrane bound protein on the same or neighboring cells. In order to understand the precise immunological role played by this protease in the thymus, future studies will be directed toward identifying its substrates (page 427). In view of Kim et al. and the lack of guidance provided by the disclosure for an uniformed biological activity of SEQ ID NO: 1, it appears that the biological function of SEQ ID NO: 1 is unknown at the time the invention was filed in view of the art of record and the lack of guidance for a definition of the biological activity of epithin (SEQ ID NO: 1) provided by the as-filed specification.

In addition, the applicants claim a method of producing a transgenic mouse using the construct and a method of identifying an agent that modulates the function

of a serine protease comprising an in vitro cell or a cell isolated from a transgenic animal comprising the targeting construct. It appears from the applicants' disclosure, that the only uses for the targeting construct is either for the production of a transgenic animal or production of an in vitro cell comprising the stably integrated targeted construct set forth above. However, the claimed invention does not described how to use the targeting construct set forth above because the biological function of the serine protease gene set forth in SEQ ID NO: 1 is not defined by the specification nor the art of record. This information is considered essential and is required for one skilled in the art to make and/or use the targeting construct for any method sought in the claimed invention because one skilled in the art would have to know how the serine protease gene functions in order to characterize the phenotype of a transgenic animal comprising a stably integrated construct in the serine protease gene compared to a normal animal having an endogenous serine protease gene. In addition, one skilled in the art would need to know the biological function of SEQ ID NO: 1 for use in any in vitro method of identifying agents that modulate the serine protease gene. Since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., ed.), Birkhauser, Boston, MA, pp. 492-494), it would require an undue amount of experimentation for one skilled in the art to arrive at the function of the serine protease gene. In view of the breadth of the serine protease family; the unknown function of the SEQ ID NO: 1; and the unpredictability of predicting biological

activity of a protein based on its peptide sequence, it would take one skilled in the art an undue amount of experimentation to reasonably correlate from predicted protein structure and expression of epithin in the thymus to a biological activity of the nucleotide sequence set forth in SEQ ID NO: 1. Therefore, the as-filed specification does not provide sufficient guidance for one skilled in the art to use the serine protease gene set forth in SEQ ID NO: 1 for any part of the claimed invention.

Furthermore, even if the applicants are able to overcome the 112 written description and enablement rejection set forth above for the biological activity of SEQ ID NO: 1, the art of record provides major concerns with the production of a transgenic non-human animal. The specification discusses that the invention features a genus of transgenic non-human animals comprising a disruption in a serine protease gene and goes on to contemplate techniques for producing the transgenic animals (pages 11-13 and pages 15-18). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection. In addition, the as-filed specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA (page 15).

The specification requires that the starting material, which is a targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker, be used in a method of making a transgenic non-human mammal comprising a disruption of a serine protease gene. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (pages 11-13 and 15-18). For example, a transgene can be

introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) A vector comprising the cDNA encoding SEQ ID NO: 1 and injected the vector into ES cells derived from 129/olaHsdby substrain (pages 51-52). Furthermore, the disclosure provides sufficient characterization of different parts of the mice expressing LacZ (pages 52-54). The as-filed specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate serine protease.

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great

interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic animal comprising a disruption of a serine protease gene. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any method of producing transgenic mammals comprising disruption of a serine protease gene. However, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a targeting construct described above is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human animal.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic animal comprising a transgenic sequence encoding a disrupted serine protease, which expresses the transgenic sequence such that a phenotype. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic mammal of the invention other than LacZ expression in a mouse. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic animal comprising the targeted construct set forth above.

[Note that although the claimed transgenic animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene (e.g. disrupted serine protease) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human animals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic animals. This is because of the art of transgenic is not predictable art with respect

to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammal comprising a transgene of interest (e.g. disrupted serine protease); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. disrupted serine protease) as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic mammal using microinjection of transgene into germ line and producing a transgenic mammal which comprises a targeting construct described above and which expresses the disrupted protein in the transgenic animal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host

species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic animal that expresses a disrupted serine protease, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic animal comprising a targeting construct set forth above and which expresses the disrupted protein in the transgenic animal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

Furthermore, with respect to claims 1-16, which are directed to using a targeting construct in a method for producing a transgenic non-human animal comprising a targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker, the as-filed specification does not provide sufficient guidance for one skilled in the art to make and/or use any polynucleotide sequence that is homologous to a serine protease gene. The

as-filed specification provides sufficient guidance for one skilled in the art to make and/or use a targeting construct comprising SEQ ID NOs: 3 and 4. However, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be enabled to reasonably correlate from one targeting construct to any other targeting construct comprising polynucleotide sequences homologous to a serine protease gene, since at the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas. The state of the art in 1998, exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, Chiu displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of targeting constructs comprising polynucleotide sequences homologous to a serine protease) as recited in the claims, particularly in view of the reasons set forth above and the breadth of the claims, one skilled in the art would not have known how to make and/or use the claimed invention so that it would operate as intended, *e.g.* said targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker for use in a method of producing a transgenic mouse that expresses a disrupted serine protease.

In addition with respect to claim 10, wherein in view of the breadth of the claim, the term cell encompassing any cell (e.g. somatic, embryonic, and germ-line) and introducing the cell into any target site in a non-human transgenic animal. The state of the art, as discussed above, teaches how to use a mouse pro-nuclei or a mouse embryonic stem cell in a method of producing a transgenic mouse, however the state of the art does not provide sufficient guidance for how to use any other cell (somatic cell, e.g. lung cell, muscle cell) in a method of producing a transgenic non-human animal. Furthermore, the state of the art teaches that stem cells are injected into a blastocyst or a mice embryo or that a pro-nuclei cell is injected into a fertilized oocyte, however, the disclosure and the art of record do not provide sufficient guidance for how to introduce a cell into any part of a non-human animal other than injecting a pro-nuclei cell into a fertilized oocyte or a blastocyst. Thus, in view of the breadth of the claim the disclosure is only enabled for injecting a pro-nuclei of an non-human animal into a fertilized oocyte or injecting a genetically modified mouse embryonic stem cell into a blastocyst of a developing embryo of a mouse.

In conclusion, in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material, a transgenic non-human animal, the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human animal, the claimed invention is not enabled. Furthermore, the working examples for the demonstration or the reasonable correlation to the production of any transgenic non-human animal, in particular when the expression of the must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human animal, and the breadth of the claims drawn to any transgenic non-

human animal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 5-9 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "derived" in claims 8, 9, and 15 is a relative term, which renders the claim indefinite. The term "derived" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, since the disclosure does not provide a definition for the term, the metes and bounds of the term are not defined. It is not apparent to one skilled in the art if a cell derived from a non-human transgenic animal would still comprise a disruption in a serine protease gene as the starting material (cell comprising a disruption in a serine protease gene). Suggest amending the claims as follows: A cell derived from the non-human transgenic animal of claim 8, wherein the cell comprises a targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker.

Note: Claim 8 is considered rejected because when reading the claim as a whole; claim 8 is considered part of claims 9 and 15.

The phrase "a cell comprising a disruption in a serine protease gene" in claims 5-7 and 11-16 is a relative phrase, which renders the claim indefinite. The phrase "a cell comprising a

disruption in a serine protease gene" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims do not distinctly point out and claim the intended subject matter. More specifically, the disclosure defines "disruption" of a target gene when a fragment of genomic DNA locates and recombines with an endogenous homologous sequence, these disruptions may include insertions which include the insertion of entire genes, which may be animal, plant, fungal, etc." (page 7). However, the claims read on a cell comprising a disrupted serine protease gene through a naturally occurring disruption in the cell. For example, an animal can have cells comprising a disruption in a serine protease gene without using the targeting construct (e.g. genetic mutation). Suggest amending the claims as follows: A cell comprising a targeting construct, wherein the targeting construct comprising a) a first polynucleotide sequence homologous to a serine protease gene, b) a second polynucleotide sequence homologous to the serine protease gene, and c) a selectable marker and wherein the targeting construct is stably integrated in an endogenous serine protease gene.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
6/17/02

DAVE T. NGUYEN
PRIMARY EXAMINER